2. INVENTIVE STEP

2.1 Claims 1 to 38

The Examiner argued that the problem underlying the present application has been described already in the documents D1 to D4.

However, it is respectfully submitted that we enjoy the priority of February 13, 1998 for the claimed subject matter. Documents D1 and D2 have been published after the relevant priority date and therefore cannot be considered to represent the prior art. At the priority date, only documents D3 and D4 had appeared. These documents contained a hint as to the mechanistic basis of the problem, but no indication about how this could be remedied in concrete technical terms.
In other words, the relevant prior art did not suggest any solution how the problem referred to in D3 and D4 could be solved in technical terms.

2.2. The Examiner argued further that not only the problem was described in the prior art, but also the solution was suggested and even more the molecular basis of that suggestion was explained.

We do not agree with the Examiner, because the establishment of the mechanism of discrimination against AZTMP was not achieved until the high resolution structures of yeast and E. coli thymidylate kinases were solved as complexes with the bisubstrate analog TP_5A, allowing a comparison and identifying the similar roles for arginine residues in the catalytic mechanism. It was the discovery that these catalytic arginines are located in different parts of the structure of the two enzymes which led to an understanding of the reasons for the dramatic differences in the efficiency of AZTMP phosphorylation. Thus, the present invention relates to modifications altering the function of thymidylate kinases that are guided by the teachings from the high resolution structures. Accordingly, the realization of the goal of specifically improving the AZTMP

phosphorylation activity of human thymidylate kinases is described in the application for the first time. This view is also supported by the publication of documents D1 and D2 (co-authored by the inventors) corresponding to the invention in well-accepted scientific journals.

2.3 Claims 29 and 30

The Examiner argued that claims 29 and 30 cannot be considered as inventive, since they are only based on the well-known action of thymidylate kinase and are not depending on the modified kinases of the present application.

We do not agree with the Examiner because claims 29 and 30 refer to the polypeptide of claim 21. The polypeptide of claim 21 is encoded by the polynucleotide of claim 14 or obtainable by the method of any one of claims 1 to 13 or 19 and 20, all of which relate to a modified polypeptide. Therefore, claims 29 and 30 have to be considered as inventive.

2.4 The Examiner argued that inhibitors, which are obtainable by the method of claims 31 or 32, but which have been obtained by other means, are already known. They could be, for instance, a substrate analog such as TP_5A. The Examiner argued further, that therefore claim 35 does not seem to be inventive.

We do not agree with the Examiner. Claim 35 (amended) relates to the use of the inhibitor obtainable by the method of claim 31 for the preparation of a pharmaceutical composition for inhibiting virus replication or for treating cancer. Although TP_5A and other substrate analogs might be obtainable by the method of claim 31 they cannot be considered as a pharmaceutical composition by a skilled artisan for inhibiting virus replication or for treating cancer for the following reasons:

Highly negatively charged nucleotides such as TP_5A and others of this type cannot enter cells and cannot therefore reach their target enzyme if, as is the